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(54) Title: A METHOD FOR THE PURIFICATION OF LANSOPRAZOLE

(57) Abstract: The present invention provides a method for preparing a substantially pure lansoprazole containing less than about 0.2% (wt/wt) impurities including sulfone/sulfide derivatives. The present invention also provides a process for recrystallizing lansoprazole to obtain a lansoprazole containing less than about 0.1 % (wt/wt) water.

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A METHOD FOR THE PURIFICATION OF LANSOPRAZOLE

CROSS-REFERENCE TO RELATED APPLICATIONS

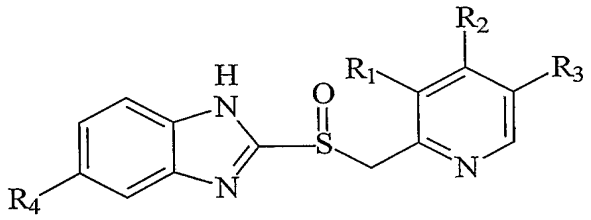
This application claims the benefit of the U.S. Provisional Application Serial Nos. 60/404,845 filed August 21, 2002 and 60/418,056 filed October 11, 2002, the disclosures of which are incorporated by reference in their entirety herein.

FIELD OF THE INVENTION

The present invention relates to a method for preparing a substantially pure 2-(2-pyridylmethyl) sulfinyl-1*H*-benzimidazole (lansoprazole) that is free of sulfone and sulfide derivatives. The present invention also relates to a method of preparing a lansoprazole containing <0.1% (wt/wt) water.

BACKGROUND OF THE INVENTION

Several substituted 2-(2-pyridylmethyl) sulfinyl-1*H*-benzimidazole derivatives are well-known gastric proton pump inhibitors. These benzimidazole derivatives include lansoprazole, omeprazole, pantoprazole, and rabeprazole. This class of benzimidazole derivatives is generally represented by the following chemical formula A:



A

U.S. Pat. No. 4,628,098 describes the generic lansoprazole compound. Lansoprazole has as its chemical name (2-[[[3-methyl-4-(2,2,2-trifluoro-ethoxy)-2-pyridinyl]methyl] sulfinyl]-*1H*-benzimidazole), i.e., when R_1 is methyl, R_2 is trifluoro-ethoxy, R_3 is hydrogen and R_4 is hydrogen.

As a characteristic shared with other benzimidazole derivatives (e.g., ompeprazole and pantoprazole), lansoprazole can inhibit gastric acid secretion, and thus commonly used as an antiulcer agent.

Several methods for preparing lansoprazole are known. The majority of these methods involve the use of a lansoprazole precursor that contains a thioether group. The thioether group is oxidized in the last step of preparation to form the lansoprazole.

U.S. Pat. Nos. 4,628,098 and 5,578,732 (the '732 patent) describe the oxidation of the thioether group using m-chloro-perbenzoic acid as the oxidizing agent. However, the use of m-chloro-perbenzoic acid often results in a non-selective oxidation of the thioether group. The '732 patent further describes an oxidation method with hydrogen peroxide (H_2O_2) in the presence of a specific vanadium catalyst. Other patents such as ES 2105953, WO 0121617, ES 2063705, U.S. Pat. No. 6,313,303, WO9947514, WO0168594 describe the use of other oxidation reagents and/or other catalysts. None of these oxidation methods result in selective oxidation of the thioether group.

In addition, the preparation of lansoprazole by conventional methods is always accompanied by the formation of small quantities of the corresponding sulfone derivative as an impurity. For example, U.S. Pat. No. 6,180,652 (the '652 patent) describes the presence of sulfone derivative. Formation of sulfone derivative brings about the drawback of low yield of the desired sulfoxide.

Although attempts have been made to separate the sulfone derivative from lansoprazole, it is not a simple task, given their very similar structures and physicochemical properties. For this purpose, the '652 patent describes a method which permits separation of lansprazole from its sulfone derivative. An acetone complex of the lansoprazole salt is purified in this method.

Lansoprazole and other 2-(2-pyridylmethyl) sulfinyl-benzimidazole derivatives tend to lose stability and undergo decomposition when contaminated with traces of a solvent, particularly water, in their crystal structure. It is desirable that the

benzimidazole crystals be solvent free (i.e., residual solvent should be reduced to a minimum).

The '732 patent describes the crystallization of lansoprazole using a ethanol:water solvent system (vol:vol of ethanol:water is 9:1). U.S. Pat. No. 6,002,011 (the '011 patent) describes the crystallization of lansoprazole from the same ethanol:water system, containing traces of ammonia (0.03 mole NH_4OH: 1 mole lansoprazole). The '011 patent discloses a reslurry method in water, which permits to obtain more stable "solvent free" lansoprazole. The '011 patent fails to disclose the level of purity for lansoprazole. In addition, the ethanol and water are difficult to eliminate. Even after intensive drying, lansoprazole still contains solvent and is unstable under storage.

There is continuing need to obtain 2-(2-pyridylmethyl) sulfinyl-1*H*-benzimidazoles (e.g., lansoprazole) that are free of contaminants including sulfone and sulfide derivatives. There has also been a long-felt need for a method to prepare 2-(2-pyridylmethyl) sulfinyl-1*H*-benzimidazoles (e.g., lansoprazole) having reduced water content (<0.1% wt/wt water).

We discovered that "solvent free" lansoprazole can be obtained by the crystallization from different solvents. Lansoprazole obtained by this method of crystallization can be dried to <0.1% water, as is required by the USP forum.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides a method of purifying lansoprazole, especially to 0.20% impurites or less, which method includes the steps of: providing a solution of lansoprazole in a solvent selected from an organic solvent, especially an alcohol (especially ethanol), acetone, 2-butanone, dimethyl-formamide and tetrahydrofuran, or a mixture of organic solvent and water in the presence of an amine compound, especially ammonia, ammonium hydroxide, diethyl amine, triethyl amine, or methyl amine, especially in equimolar ratio (or higher) to the lansoprazole; combining the provided solution with an acid, especially acetic acid, formic acid, or hydrochloric acid; and isolating the purified lansoprazole. When the solvent is a mixture of organic solvent and water, the ratio of organic solvent to water is especiallyabout 0.2:1 to about

3:1 and the volume-to-weight ratio of such solvent to lansoprazole is about 17:1 to about 5:1, especially about 11:1.

In another aspect, the present invention relates to a method of preparing a lansoprazole containing less than about 0.1% (wt/wt) water (i.e. for desolvation lansoprazole) comprising the steps of: crystallizing, optionally in the presence of an amine compound in a mole ratio of about 0.05:1 relative to lansoprazole, especially at 50°C or less, a lansoprazole (which can be wet or dry) from solution in a solvent that is an organic solvent, especially acetone, 2-butanone, methanol, dimethyl-carbonate, and diethyl-carbonate, or a mixture of an organic solvent and water; and isolating the lansoprazole containing less than about 0.1% (wt/wt) water. Crystallization can be effected by lowering the temperature of the solution, combining the soloution with water (less than about 20% vol/vol), or both.

In still a further aspect, the present invention relates to a method of purifying lansoprazole to obtain lansoprazole having less than about 0.1%, wt/wt, water comprising the steps of: providing a solution of lansoprazole in a solvent selected from an organic solvent, especially ethanol, or a mixture of organic solvent and water in the presence of an amine compound, wherein the amine compound is present at a ratio of about 1:1, mole:mole, relative to lansoprazole; combining the provided solution with an acid, especially acetic acid, formic acid, or hydrochloric acid; isolating the lansoprazole; dissolving the isolated lansoprazole in an organic solvent selected from the group consisting of acetone, 2-butanone, methanol, dimethyl-carbonate, and diethyl-carbonate (especially acetone), optionally in the presence of an amine compound; and isolating the purified lansoprazole having less than about 0.1%, wt/wt, water.

In yet another aspect, the present invention relates to lansoprazole having less than 0.20 wt-% impurities, especially when the water content is 0.1% by wt or less.

In a further aspect, the present invention relates to lansoprazole having less than 0.20 wt-% combined sulfide and sulfone derivatives, especially when the water content is 0.1 wt-% or less.

In still a further aspect, the present invention relates to lansoprazole having less than 0.10% wt-% of either sulfone or sulfide derivative, especially in combination with a water content of 0.1 wt-% or less.

DETAILED DESCRIPTION OF THE INVENTION

As used herein "LNPS" refers to the sulfide-containing starting compound for lansoprazole preparation. The chemical name for LNPS is 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]thio]-1*H* benzimidazole. "LNP" refers to lansoprazole which has the chemical name of 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl-1*H* benzimidazole. The present invention provides a "substantially pure" lansoprazole. Substantially pure lansoprazole contains less than about 0.10% (wt/wt) sulfone derivative and less than about 0.10% sulfide derivative.

Water is not considered an imputity per se, but its presence in lansoprazole is undesirable. The present invention also provides lansoprazole that contains less than about 0.1% (wt/wt) water, referred to as "solvent free" (i.e. desolvated) lansoprazole.

Unless otherwise stated, % and % (wt/wt) refer to percent on a weight basis.

As used herein in connection with a numerical quantity, "<" refers to less than.

In accordance with the present invention, 2-[[3-methyl-4-(2,2,2-trifluoro ethoxy)-2-pyridinyl]thio]-1*H* benzimidazole (LNPS) is used as a starting material for preparation of 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl-1*H* benzimidazole and is dissolved in an organic solvent or a mixture of organic solvent with water. Any residue of the LNPS remaining in the final product is an impurity and difficult to remove.

Exemplary organic solvents suitable for use in the practice of the present invention include alcohols such as ethanol, methanol, n-propanol, i-propanol; ketones such as acetone and 2-butanone; dimethyl-formamide; tetrahydrofuran; and the like. Preferably, the organic solvent is ethanol.

In particular embodiments, mixtures of an organinc solvent listed above with water can be used. When mixtures of organic solvent and water are used, different volume ratios (vol/vol) of organic solvent and water can be used. The organic solvent/water ratio can vary between about 0.2:1 to 3:1. Preferably, the solvent/water ratio is about 1.5:1. Use of larger solvent/water ratios may result in poor crystallization yields.

When mixtures of an organic solvent and water are used, the overall ratio, on a volume per weight basis, of solvent/water (i.e., organic solvent + water) to lansoprazole

ratio can vary between about 17:1 to about 5:1 (vol:wt). Preferably, the ratio of solvent/water to lansoprazole is about 11:1 (vol/wt).

Amine compounds are used in the practice of the present invention. The overall ratio, on a mole basis, of amine compound to lansoprazole (mol/mol) can vary between about 17:1 to about 1:1. Preferably, the amine compound:lansoprazole (mol/mol) ratio is about 7:1. Exemplary amine compounds useful in the practice of te present invention include ammonia, ammonium hydroxide, diethylamine, triethylamine, methylamine and the like. Preferably, the amine compound is ammonium hydroxide.

Preferably, ammonium hydroxide is present at a mol/mol ratio to lansoprazole of about 1:1 to about 7:1. Crystallization of lansoprazole under such conditions permits a good separation of lansoprazole from impurities, especially sulfone and/or sulfide derivatives.

In one embodiment, the present invention provides a crystallization purification method for purifying lansoprazole. Crystallization of lansoprazole from solution in an organic solvent or a mixture of organic solvent and water in the presence of an amine compound according to the crystallization purification method of the present invention results in substantially pure lansoprazole.

In the present invention, purification of lansoprazole by crystallization is achieved by acidifying (i.e. combining with acid) a solution of lansoprazole in an organic solvent or a mixture of organic solvent and water. The acid combined can neutralize the amine compound during the crystallization of lansoprazole.

Exemplary acids combined to crystallize lansoprazole include acetic acid, formic acid, hydrochloric acid (HCl) and the like. Preferably, the acid is acetic acid.

Although the purified lansoprazole obtained by the above-mentioned crystallization purification process is substantially pure and can be advantageous, it does not necessarily contain <0.1% water in accordance with the USP forum. As mentioned previously, water can have a negative impact on the long-term stability of lansoprazole (U.S. Pat. No. 6,002,011).

Thus, in another embodiment of the present invention, a method for reducing the water (i.e. desolvating) lansoprazole is provided. In this embodiment, the water content of lansoprazole, especially substantially pure lansoprazole, can be reduced to <0.1% water by crystallization from organic solvent.

Exemplary crystallizing organic solvents for obtaining lansoprazole having <1%, wt/wt, water include methanol, dimethyl-carbonate, diethyl-carbonate, acetone, 2-butanone and the like. Preferably, such crystallizing organic solvents are methanol, dimethyl-carbonate and diethyl-carbonate. Most preferably, such crystallizing organic solvent is acetone.

Crystallization of lansoprazole to obtain lansopraolze having <0.1% water can be and preferrably is carried-out in the presence of an amine compound. Exemplary amine compounds include ammonia, ammonium hydroxide, diethylamine, triethylamine, methylamine and the like. Preferably, the amine compound is ammonium hydroxide.

Preferably, in this embodiment, the mole ratio of amine compound to lansopraozle (mole:mole or mole/mole) is about 0.05:1.

Preferably the lansoprazole to be desolvated is completely dissolved in the solvent before crystallization. The dissolution of lansoprazole can be promoted by the presence of small amounts of water. The presence of a small amout of water can be insured by using wet lansoprazole from the previously mentioned purification step or by adding <20% (vol/vol) water to the solvent.

The dissolution of lansoprazole to be desolvated can be performed at the crystallization solvent reflux temperature. Preferred dissolution temperatures are lower than the reflux temperature, given the reported instability of lansoprazole at higher temperatures. Preferably, the dissolution temperature does not exceed 50°C.

The crystallization yield of lansoprazole can be improved by cooling or by removing solvent or water from the crystallization system. One skilled in the art would appreciate the techniques used to remove water from a mixture of organic solvent and water include, e.g., azeotropic distillation.

The present invention can be illustrated by the following nonlimiting examples.

Example 1

Preparation of Lansoprazole Crude

Into a flask 1L ethanol was charged and cooled under stirring to 5°C. Under mixing 200 grams 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]thio]-1*H* benzimidazole (LNPS) and 3 grams vanadium acetyl acetonate were added. 110 grams *tert*-butyl-hydroperoxide solution were dropped slowly into the suspension. The suspension was maintained under mixing during 4 hours. 40 grams of Na_2SO_3 dissolved

in 400 mL water were added. Separate solid phase by vacuum filtration and dry. 165 grams of LNP crude were obtained (yield 79 %).

Sulfone 0.3%

LNPS 0.3%

Chromatographic purity method of lansoprazole monograph in USP Forum Vol. 26(5) [Sept.-Oct. 2000].

HPLC Condition:

Column:	C18
Mobile phase:	Gradient of triethylamine in water with acetonitrile
Flow:	0.8 mL/min
Detection:	285 nm

This chromatographic assay has the detection sensitivity of less than 0.1% impurities in LNP.

Example 1A

Preparation of Lansoprazole crude

Into a flask 1L ethanol (95%) was charged and cooled under stirring to 5°C. Under mixing 200 grams 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl] thio]-1H benzimidazole (LNPS) and 3 grams vanadium acetyl acetonate were added. 110 grams *tert*-butyl-hydroperoxide solution were dropped slowly into the suspension. The suspension was maintained under mixing during 6 hours. 40 grams of Na_2SO_3 dissolved in 400 ml water were added.

1L of water (pH was about 8-8.5; the pH was adjusted by the addition of NH_4OH) was added to the suspension and the suspension was further mixed for 17 hours at 25°C. The suspension was cooled to 5°C and the solid phase separated by vacuum filtration then dried. 178 grams of LNP crude were obtained (yield 85 %). Sulfone 0.15%.

Example 2

Purification of Lansoprazole

In a 0.25 L flask 67.5 mL ethanol 95%, 15 mL of ammonium hydroxide (NH_4OH) 24% and 45 mL water were charged and cooled under stirring to 5°C. Under mixing 10 grams lansoprazole crude were added and heated to 52°C to dissolution. 1

gram of active carbon was added to the slightly turbid solution and maintained a short time at 49°C. The carbon was separated on a filter and the cake washed with a mixture of 14 mL ethanol and 12 mL water. The solution was cooled and lansoprazole was precipitated by the addition of 3.75 mL acetic acid. The suspension was cooled to 10°C and filtered. The product was washed with water and ethanol and dryed. 8.7 grams of lansoprazole pure were obtained (yield: 89%). Sulfone 0.05%, LNPS under the detection limit.

The above-described procedure was applied in other examples where the solvent and/or the amine was different. The following table is illustrative for these examples:

Example	Solvent	water	Amine	Yield	Sulfone	LNPS
		yes/no		%	%	%
3	i-propanol	no	NH_4OH	52.7	0.03	0.02
4	Ethanol	no	NH_4OH	46.5	0.07	<DL[1]
5	n-propanol	yes	NH_4OH	91.5	0.08	0.04
6	i-propanol	yes	NH_4OH	90.8	0.07	<DL
7	Ethanol	yes	Triethylamine	87.6	0.05	<DL
8	i-buthanol	yes	Triethylamine	80.7	0.06	<DL

[1] less than detection limit

Example 9

Preparation of Lansoprazole Containing <0.1% (wt/wt) Water

In a 0.25L flask 29.8 grams wet LNP crystal and 30 mL acetone were charged. The suspension was heated to 52°C and 150 mL acetone was dropped until a clear solution was obtained. The solution was cooled to 10°C and concentrated until the weight of the reaction mass was 48.5 grams. The solid was separated by filtration and washed with 20 mL cold acetone. After drying 18.58 grams product were obtained (yield: 91%). Content of water according to Karl Fischer test 0.05%.

Similar to example 3, the following other examples were performed:

Examples	Solvent	Yield	Water
		%	%(KF[1])
10	Dimethylcarbonate	87.5	0.04

11	2-butanone	88.5	0.03
12	Methanol	72%	0.06

[1]Karl Fisher method for Water determination is the USP method as written in USP Forum Vol. 26(5) [Sept.- Oct. 2000].

Example 13

Preparation of Lansoprazole Containing <0.1% (wt/wt) Water

In a 0.1 L flask 4 grams dry LNP crystals and 60 mL acetone containing 15% water were charged. The solution was maintained under mixing at 25°C for 17 hours. The solution was concentrated to 15 grams and filtered. After drying 3.4 grams product were obtained (yield: 84.7%). Content of water according to Karl Fischer test: 0.06%.

Example 14

Preparation of Lansoprazole Containing <0.1% (wt/wt) Water

In a 50 mL flask 11.6 mL acetone, 3.1 mL water and 0.05 mL NH_4OH were charged. The solution was heated to 45°C and under mixing 5.8 grams of LNP crystal were charged. The solution was heated to 61°C and immediately cooled to 5-10°C. After filtration and drying 5.0 grams product was obtained (yield: 87%). Content of water according to Karl Fischer test: 0.03%.

Example 15

Lansoprazole (5.0 grams) was dissolved in 30 ml of acetone, containing 15 volume % of water, at heating at reflux. Water (30 ml) was added dropwise for 5 min to the clear solution. After cooling to room temperature the slurry was filtered, giving after drying 4.5 grams of the product (yield: 90%). Content of the water according to Karl Fischer test was 0.08%.

Example 16

Lansoprazole (5.0 grams) was dissolved in 30 ml of acetone, containing 15 volume % of water, at heating at reflux. Water (60 ml) was added dropwise for 5 min to the clear solution. After cooling to room temperature the slurry was filtered, giving after

drying 4.6 grams of the product (yield: 92%). Content of the water according to Karl Fischer test was 0.08%.

A number of embodiments of the present invention have been described. The present invention is not to be limited in scope by the specific embodiments described herein. It will be understood that various modifications may be made without departing from the spirit and scope of the invention. Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

What is claimed is:

1. A method of purifying lansoprazole, comprising the steps of:

a) providing a solution of lansoprazole in a solvent selected from an organic solvent or a mixture of organic solvent and water in the presence of an amine compound;

b) combining the provided solution with an acid, and

c)isolating the purified lansoprazole.

2. The method of claim 1 wherein the amine compound is present in 1:1, mole:mole, ratio relative to the lansoprazole.

3. The method of claim 1, wherein solution is in an organic solvent selected from the group consisting of an alcohol, acetone, 2-butanone, dimethyl-formamide and tetrahydrofuran.

4. The method of claim 4, wherien the organic solvent is the alcohol ethanol.

5. The method of claim 1, wherein the amine compound is selected from the group consisting of ammonia, ammonium hydroxide, diethylamine, triethylamine and methylamine.

6. The method of claim 5 wherein the amine compound is ammonium hydroxide.

7. The method of claim 6 wherein the ammonium hydroxide is present at a mol/mol ratio to lansoprazole of greater than 1.

8. The method of claim 1 wherein the acid combined is selected from the group consisting of acetic acid, formic acid, and hydrochloric acid.

9. The method of claim 8 wherein the acid is acetic acid.

10. A method of preparing a lansoprazole containing less than about 0.1% (wt/wt) water, comprising the steps of:

a) crystallizing a lansoprazole from solution in a solvent that is an organic solvent or a mixture of an organic solvent and water; and

b) isolating the lansoprazole containing less than about 0.1% (wt/wt) water.

11. The method of claim 10 wherein the lansoprazole of step a) is crystalline.

12. The method of claim 10 wherein the lansoprazole of step a) is dry.

13. The method of claim 10 wherein the lansoprazole of claim step a) is wet.

14. The method of claim 10, wherein the organic solvent is selected from the group consisting of acetone, 2-butanone, methanol, dimethyl-carbonate, and diethyl-carbonate.

15. The method of claim 14 wherien the organic solvent is acetone.

16. The method of either of claims 10 or 15 wherein the crystallization is effected by adding water to the solution.

17. The method of claim 10 wherein the crystallization step is performed at a temperature of about 50^0C or less.

18. The method of claim 10 further comprising the step of cooling subsequent to the crystallization step.

19. The method of claim 10 wherein ammonium hydroxide is added before or in the course of the crystallization step.

20. A method of purifying lansoprazole to obtain lansoprazole having less than about 0.1%, wt/wt, water comprising the steps of:

a) providing a solution of lansoprazole in a solvent selected from an organic solvent or a mixture of organic solvent and water in the presence of an amine compound, wherein the amine compound is present at a ratio of about 1:1, mole:mole, relative to lansoprazole;

b) combining the provided solution with an acid;

c) isolating the lansoprazole;

d) dissolving the isolated lansoprazole in an organic solvent selected from the group consisting of acetone, 2-butanone, methanol, dimethyl-carbonate, and diethyl-carbonate; and

e) isolating the purified lansoprazole having less than about 0.1%, wt/wt, water.

21. The lansoprazole made by the method of any of claims 1, 10, and 20.

22. Lansoprazole containing less than 0.20% (wt/wt) impurities.

23. The lansoprazole of claim 22 containing less than 0.1%, wt/wt, water.

24. Lansoprazole containing less than 0.20%, wt/wt, combined sulfide and sulfone derivatives.

25. The lansoprazole of claim 24 containing less than 0.1%, wt/wt, water.

26. Lansoprazole containing less than 0.10%, wt/wt, sulfide derivative.

27. The lansoprazole of claim 26 containing less that 0.1%, wt/wt, water.

28. Lansoprazole containing less than 0.10%, wt/wt, sulfone derivative.

29. The lansoprazole of claim 28 containing less than 0.1%, wt/wt, water.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/26544

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 6 002 011 A (ISHIDA TORU ET AL) 14 December 1999 (1999-12-14) cited in the application claims example 1	10-19, 21-29 1-9,20
Y	US 6 268 502 B1 (JEREB DARJA ET AL) 31 July 2001 (2001-07-31) claim 1; example 1	1-9,20
Y	US 6 166 213 A (BANKS BENJAMIN NEWTON ET AL) 26 December 2000 (2000-12-26) claim 5; example 2	1-9,20
X	US 5 578 732 A (KATO MASAYASU ET AL) 26 November 1996 (1996-11-26) cited in the application example 4	10-19, 21-29

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2003	26/11/2003

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